PATENT COOPERATION TREATY

# PCT

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# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference 49324-296 | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No. PCT/CA2004/000505 | International filing date *(day/month/year)* 02.04.2004 | Priority date *(day/month/year)* 02.04.2003 |
| International Patent Classification (IPC) or national classification and IPC A61K9/127, A61K9/51, A61K31/4745, A61K31/7072, A61K47/02 | | |
| Applicant CELATOR TECHNOLOGIES, INC. et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☒ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 19.01.2005 | 25.07.2005 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Albrecht, S Telephone No. +49 89 2399-7864 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/000505

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

| | |
|---|---|
| **Description, Pages** | |
| 1-26 | as originally filed |
| **Claims, Numbers** | |
| 1-19 | received on 09.05.2005 with letter of 04.05.2005 |
| **Drawings, Sheets** | |
| 1/6-6/6 | as originally filed |

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,3-19 (3-19 partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1,3-19 (3-19 partially) are so unclear that no meaningful opinion could be formed *(specify)*:

**see separate sheet**

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 2-19 (3-19 partially) |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 2-19 (3-19 partially) |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-19 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Box No. VI Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

III.1. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the pH of the claimed composition in terms of the result to be achieved, namely a pH which maintains the agent in its active lactone ring form. Such a definition is only allowable if the invention can only be defined in such terms (PCT Preliminary examination Guidelines, chapter 5.35). In this instance, however, such a formulation is not allowable because the pH can be defined more precisely without unduly restricting the scope of claim 1. Mutatis mutandis dependent claims 3-19.

Accordingly, novelty and inventive step issues cannot be discussed for claim 1, whereas the examination of claims 3-19 will be limited to pharmaceutical compositions having a pH between 6.0 and 8.0.

Re Item V

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The documents cited in the Search Report (SR) are consecutively numbered D1-D13 in this communication; this numbering will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

**V.1. Novelty**

Claim 2 appears to be novel over the available prior art. Under the proviso of item III.1, claims 3-19 also appear to be novel over the available prior art.

**V.2. Inventive step (claims 3-19 under the proviso of item III.1)**

a) D3, which is considered to represent the most relevant state of the art, discloses liposomes containing manganese ions (300mM) and topotecan, the loading of the latter being accomplished by means of an ionophore-mediated proton gradient. As a result of this, liposomes with an acidic internal pH are provided, which permits the topotecan to maintain its active lactone form.

b) The subject-matter of claims 2-19 differs from D3 in that the in D3 described compositions present an acidic intraliposomal pH, whereas the pH of the external solution is not specified.

c) The technical problem to be solved by the present invention consists of providing alternative pharmaceutical compositions of active agents having a lactone ring and requiring such a ring for their pharmacological activity, whereby the composition maintains the active agent in its active ring-closed form at a pH in the physiological range (between 6.0 and 8.0).

d) The solution proposed by the applicant constitutes a composition comprising the active agent in combination with a transition metal ion.

e) Prior art does not give any indication to use metal transition ions in order to stabilise the lactone ring of active agents which require such a closed ring for their pharmacological activity. In addition, the applicant has provided evidence that the technical problem can be solved by the present invention.

f) Therefore, claims 2-19 may be regarded as involving an inventive step in the sense of Article 33(3) PCT.

**Re Item VI**

**Certain documents cited**

Certain published documents

| Application No Patent No | Publication date *(day/month/year)* | Filing date *(day/month/year)* | Priority date *(valid claim)* *(day/month/year)* |
|---|---|---|---|
| WO03/028697 | 10/04/03 | 03/10/02 | 03/10/01; 17/12/01; 15/02/02; 07/03/02; 09/07/02 |
| WO02/028696 | 10/04/03 | 03/10/02 | 03/10/01; 17/12/01; 15/02/02; 23/04/02; 07/08/02; 06/09/02 |

## Claims

1. A pharmaceutical composition comprising an agent which is active when substantially in lactone ring form and a transition metal ion, said composition having a pH such that conversion of said lactone to a carboxylate would normally result, wherein said ion is present at sufficient concentration to stabilize said lactone.

2. The composition of claim 1 wherein the pH of the preparation is between 6.0 and 8.0.

3. The composition of claim 1 or 2 wherein the active agent and the transition metal ion are stably associated with one or more delivery vehicles selected from the group consisting of lipid carriers, liposomes, lipid micelles, lipoprotein micelles, lipid-stabilized emulsions, cyclodextrins, polymer nanoparticles, polymer microparticles, block copolymer micelles, polymer-lipid hybrid systems and derivatized single chain polymers.

4. The composition of any of claims 1-3 wherein at least 40 mole % of the active agent is present in the ring-closed, lactone form at physiological pH.

5. The composition of claim 4 wherein at least 50 mole % of the active agent is present in the ring-closed, lactone form at physiological pH.

6. The composition of any of claims 1-5 wherein the active agent is camptothecin or a derivative thereof.

7. The composition of claim 6 wherein the camptothecin is a water-soluble derivative.

8. The composition of claim 7 wherein the water-soluble derivative is selected from the group consisting of topotecan, irinotecan and lurtotecan.

9. The composition of any of claims 1-8 wherein the active agent and the metal are at a concentration of greater than 100 μM.

10. The composition of any of claims 1-9 wherein said ion is of transition metal is selected from the group consisting of Cu, Zn and Co.

11. The composition of claim 10 wherein the transition metal is Cu.

12. The composition of any of claims 3-11 wherein the delivery vehicle is a liposome.

13. The composition of claim 12 wherein the liposome is a large unilamellar liposome.

14. The composition of any of claims 3-11 wherein the delivery vehicle is a liposome and the transition metal ion is Cu+2.

15. The composition of claim 14 wherein the active agent is a camptothecin or a derivative thereof.

16. The composition of claim 15 wherein the camptothecin is a water-soluble derivative selected from the group consisting of lurtotecan, topotecan and irinotecan.

17. The composition of any of claims 3-11 wherein the delivery vehicle is a polymer nanoparticle.

18. The composition of claim 17 wherein one or more polymers making up the nanoparticle are complexed with a transition metal ion.

19. The composition of claim 18 wherein the nanoparticle comprises a stabilizing lipid.